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This symposium focuses on exertional heatstroke, with emphasis on predisposing factors, clinical observations, diagnosis, treatment and recovery. The serious challenge to cardiovascular stability presented by exercise hyperthermia and some aspects of regulatory failure were reviewed in the introduction. The intent to focus on the pathophysiology of the cell in this manuscript is not to downplay the seriousness of the systemic condition, but to try to understand how heat stress is translated into heat strain at the cellular level. If this is accomplished, it may stimulate further interest in the impact of heat on the cell as a model for other factors which alter membrane integrity and permeability, lead to new experimental paradigms, and improve the diagnosis and treatment of disorders such as toxic, hypovolemic, or ischemic shock. This review also may stimulate interesting applications to more subtle threats to homeostasis such as chronic exercise, hypohydration and thirst, ion imbalance, and sleep deprivation. Since the original article,

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Heatstroke Pathophysiology:

The Energy Depletion Model

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Abstract

This symposium focuses on exertional heatstroke, with emphasis on predisposing factors, clinical observations, diagnosis, treatment and recovery. The serious challenge to cardiovascular stability presented by exercise hyperthermia and some aspects of regulatory failure were reviewed in the introduction. The intent of this review, to describe how heat stress is translated into heat strain at the cellular level, is not to downplay the seriousness of the systemic condition. If we are successful, this may stimulate further interest on the impact of heat on the cell as a model for other factors which alter membrane integrity and permeability, lead to new experimental paradigms, and improve the diagnosis and treatment of other disorders such as toxic, hypovolemic or ischemic shock. This review may also stimulate interesting research regarding more subtle threats to homeostasis such as chronic exercise, hypohydration and thirst, ion imbalance, and sleep deprivation. Since the original article on heat stroke pathophysiology was published (39), we have discussed the relationship of this concept to carbohydrate metabolism (37), thirst (41), and the cellular aspects of heat illness treatment (99). This article will attempt to integrate and extend some of those ideas.

Key Words: fluid-electrolyte balance, cell membrane, glycolysis, inhibition of sodium pump, fatigue, lactic acid, potassium depletion.

Historical Perspective

There is a problem with salt and water balance that is even more vexing than the impact of hypovolemia on cardiovascular and thermoregulatory function. This relates to the pathology of exertional heat stroke in the absence of significant dehydration. The pathology depicts generalized tissue injury and degenerative organ changes consistent with increased tissue weight, congestion, edema and swollen cells (79). From this perspective, system failures in a previously healthy individual exercising *in* a hot environment are considered more often a consequence than seen as a cause of heat accumulation (79). Shibolet further reasoned (79) that when death occurs rapidly (70% of the Malamud series [59] within 24h), ..."an acute and general derangement of biochemical reactions on a cellular level seems to be implicated". This noxious and often fatal disruption of normal homeostasis by a combination of hyperthermia and exercise makes us confront the issue that is underlying and fundamental to relatively stable intracellular, extracellular, and intravascular fluid volumes, that there are cells trying to cope (energetically) with "leaky membranes." The pathological end point (swollen cells) in heatstroke suggests a battle lost.

Our prior research has led us to hypothesize that thermally-driven energy drain could limit an animal's energy supply for useful work (39). This concept has been visualized as a cycle called the Energy Depletion Model (37,39,41) and has three primary components: I. Thermally-driven neuro-muscular events such as: (a) the direct effects of increasing temperature on skeletal muscle function are manifested by increased metabolic rate (13, 24); (b) the energy cost of force

development increases approximately threefold, for each 10°C rise in temperature (67,76); (c) part of this added energy cost is due to the increase in stimulation frequency necessary in vitro to develop the same force (76); and (d) there may be increased neurotransmitter release (89) secondary to an elevated intraterminal calcium concentration (82) and a decrease in the transmembrane sodium gradient (34). II. Events occurring at the level of the cell membrane in muscle and other tissues such as: (a) membrane leakage of sodium and potassium ions and the resultant active transport activity may account for nearly half of the basal metabolism of the brain (94,35); (b) heat increases the kinetic energy of ions in solution, increases diffusion, increases the permeability of the cell to sodium ions (3), and superimposes an energy drain (transmembrane ion pumping) onto the basal metabolic rate (62); and (c) membrane permeability, as assessed by elevations in serum creatinine kinase and lactate dehydrogenase increases dramatically with a higher *rate* of change in body temperature. III. Events occurring within the cell to reduce steady-state energy levels promote fatigue and cell swelling: (a) lactic acid accumulation is closely associated with heating rate (55); (b) intracellular acidosis stimulates a Na^+-H^+ exchange across the cell membrane that, while helping to regulate intracellular pH (68), increases sodium permeability and sodium pump activity (Pump-Leak Hypothesis; [57]); and (c) mitochondrial respiratory function is inhibited by acidosis (35,96).

This thermally-driven increase in basal metabolic rate further suggests that the heat which the cell experiences (i.e. stored heat) reduces the metabolic efficiency of the cell at high core temperatures by stimulating glycolysis (37). This declining

metabolic efficiency could go undetected because it would not stimulate oxygen uptake immediately and the heat gain typically would be offset by greater heat loss. Underlying this review were four basic questions, for which we only have partial answers: 1. Why are swollen cells a common feature of heatstroke? 2. Does a thermally-driven energy drain limit the ability for useful work? 3. How is heat stress translated into heat strain at the cellular level? and, 4. Does stored heat stimulate glycolysis and reduce metabolic efficiency?

Muscle Fatigue and Rigor

The pathological picture of heatstroke suggests a fundamental problem with energy availability. Muscle fatigue is defined as a failure to sustain force or power output and is used synonymously with a decline in tension (71). Feelings of muscle weakness and fatigue are subjective symptoms of heat illness (2). In extremes of energy deficiency, muscle cannot relax and remains contracted (rigor). Slowing of relaxation is a feature of fatigued muscle (71). Muscle rigidity and rapid rigor mortis are classic features of heatstroke death (97) and the extensibility of muscle during the development of rigor mortis appears to be linearly related to the muscle ATP content (10). Rigor does not normally occur unless muscles are poisoned with iodoacetic acid (IAA) and glycolysis is inhibited (69) or no longer able to meet the existing energy demand. The stimulation of IAA poisoned muscle produces a decrement in ATP and about a 50% decline in the total adenine nucleotide content (71). Thus, a fall in cellular ATP or total adenine nucleotide content could delineate a stage in cell injury.

Stages in Cell Injury and Death in Hepatocytes

The process of cell death has been described in anoxic hepatocytes (33) as a three stage process of cell-surface bleb formation, suggesting that alterations in plasma membrane structure and function were early features of injury. Stage I was characterized by formation of numerous small blebs. Stage II was characterized by the enlargement, coalescence and fusion of small blebs into a few large terminal blebs. Near the end of stage II, cells began to swell rapidly, ending with the apparent breakdown of one of the terminal blebs. Breakdown of the bleb initiated stage III of injury coincidental with a rapid increase of nonspecific plasma membrane permeability. Recovery from stages I and II was possible with reoxygenation, but was not possible in stage III. The pathogenesis of irreversible cell injury in ischemia (27), resulting in cell death, was seen also as dysfunction of plasma membrane ion pumps, calcium influx, activation of phospholipases, and destruction of mitochondrial and plasma membrane integrity. For example, ischemia resulted in membrane phospholipid degradation (18), an increase in plasma membrane permeability (15), and a decrease of Na-K-ATPase activity (81). Whether the energy available, to maintain the appearance of a plasma membrane permeability barrier, can be gradually lost remains a central question. Certainly, there appears to be at least a three-stage process involved: loss of function tied to a reversible lowering of the cellular energy state, structural changes in the cell membrane, and irreversible structural damage (i.e. loss of the membrane permeability barrier). Perhaps there are chronic conditions predisposing to a loss of function. Possible causes to explore

are heat, electrolyte imbalance, hypotension, chronic exercise and sleep deprivation, that are all thought to predispose to heat injury.

Blood Pressure and Flow Thresholds in Brain Ischemia

A more familiar example to physiologists, and the hallmark which distinguishes heatstroke from heat exhaustion is the loss of consciousness or brain function in cerebral ischemia. Recent evidence from neuroscience (6) suggests that the immediate failure of basic functions in the ischemic brain (i.e. cessation of neuronal activity, synaptic transmission, ion pumping and energy metabolism) is critically dependent on residual blood flow, and that these functions fail at certain critical flow thresholds. For example, flattening of the EEG occurs immediately if hemispheric blood flow falls below 0.16 - 0.17 $ml \cdot g^{-1} \cdot min^{-1}$ (88,92). There is also another time dependent, lethal threshold below which tissue infarction and cell death occurs. This flow threshold for electrical failure appears to be quite fixed (8) but is not associated with an abnormal efflux of potassium (8). A lower blood flow, (0.10 $ml \cdot g^{-1} \cdot min^{-1}$), was required to elicit massive potassium efflux indicative of membrane "pump failure".

In further rat studies using bicuculline-induced continuous, generalized seizures (4), electrical failure appeared as cessation of seizure discharges while extracellular potassium remained nearly normal. Even though the rate of pumping was affected, lactic acid concentrations were elevated, phosphocreatine decreased, and the ATP concentration was close to normal. The significant difference in the blood pressure levels separating the thresholds of electrical failure (46 mmHg) and

of ion pump failure with ATP depletion (32 mmHg) suggested progressive ischemia (4). The critical factor for brain tissue function is oxygen availability, rather than blood flow. When controlled hypotension was combined with hypoxia (5), the critical levels of blood pressure, at which electrical failure and ion pump failure occurred, were elevated (78 and 65 mm Hg in hypoxia versus 46 and 32 mm Hg in normoxia). These results suggest that the thresholds change relative to the balance between energy availability and energy demand.

Hypermetabolic states likewise affect these thresholds and, in bicuculline-induced seizures, the metabolic rate is increased threefold (4). The degree of hypotension required to induce electrical failure was so moderate (1/2 of preischemic value) that it could have easily been tolerated in non-seized animals. Cabral et al (16) have reported reversible profound depression of cerebral electrical activity in hyperthermia with fixed and dilated pupils and a flat EEG. The early pathogenesis of heatstroke in conscious rabbits exposed to an ambient temperature of 40°C has been described (80). The data demonstrate that hyperthermia occurs concurrently with cerebral edema and cerebral vascular congestion. At the onset of heatstroke (coma), intracranial pressure increased from 14 to 49 torr. Intracranial hypertension in combination with a reduction in mean arterial blood pressure (MABP), produced a dramatic fall in cerebral perfusion pressure which declined in these rabbits from 80 to 19 Torr. Cerebral water content was increased and histological examination revealed brain congestion. These results suggested that the hypermetabolic states associated with hyperthermia could increase energy demand and lower the usual thresholds for injury. This may explain the higher injury rate associated with

exertion-induced hyperthermia (37,40).

Metabolic Events in Ischemic Energy Failure

The metabolic events acting as counterparts to "electrical", "ion pump" or membrane failure are not well known or substantiated (82). In sudden, total ischemia, significant decreases in phosphocreatine and ATP, as well as increases in ADP, AMP and lactate occur within 10 s. A decline in the energy charge to minimal values, indicative of complete energy failure, occurs within 5-7 minutes and is preceded (2-3 min) by marked elevations in tissue lactic acid (12-14 $umol \cdot g^{-1}$). The formation of AMP allows it to be dephosphorylated to adenosine and deaminated to inosine monophosphate. These are subsequently converted via inosine and hypoxanthine to xanthine and uric acid. As a result, the total sum of the adenine nucleotide pool is reduced. A similar loss of nucleotides was seen in the stimulation of IAA poisoned muscle (69). Resynthesis of nucleotides by de novo pathways is slow (17) and the ATP content may be reduced for several hours. This appears to enhance the significance of the increased uric acid excretion observed in heat stress. This suggests that factors associated with chronic exercise and heat stress are induce a metabolic state of glycolytic insufficiency only observed in acute preparations with poisoned muscles.

In 1974, Knochel et al. (48) found hyperuricemia and rising uric acid excretion in men, by the eleventh day of intense physical training in a hot climate. Maximal muscle tenderness coincided with creatinuria, abnormal creatine phosphokinase activity, depressed serum calcium, and elevated serum phosphorous concentrations.

The approximately 350 mg · day^{-1} excess uric acid excretion represented metabolism of approximately 2.0 g of purine precursors. Activation of AMP-deaminase was postulated, subsequent to increased AMP concentrations from increased myokinase activity. The trigger for this reaction sequence is decreased intracellular ATP concentrations (48), suggesting that chronic exposure to heat stress and exercise may produce cumulative deficits in muscle adenine nucleotide content. In an analogous fashion, fructose infused into normal subjects traps inorganic phosphate and prevents ATP resynthesis, resulting from increased uric acid formation and intracellular nucleotide depletion (58).

Double-Donnan Pump-Leak Hypothesis

Energy failure should be the event triggering dissipative ion fluxes (K^+ efflux, Na^+ and Ca^{++} influx). The suggestion that these events are triggered by blood flow and pressure thresholds does not imply a "static state". For example, in the mid-1950's physiologists (60) asked why cells did not swell when they had a high concentration of of intracellular proteins and other macromolecules exerting an osmotic pressure. Any cell containing impermeable anions, and possessing a membrane permeable to small ions such as Na^+ and Cl^-, would be expected to accumulate such ions and water (Donnan system). As recognized by Leaf (52) and as explained by MacKnight (56), "So long as the rate at which a substance crossed the membrane from the extracellular fluid into the cell was equaled by the rate at which it was passed from the cell to the extracellular fluid, that substance in effect would be held in the extracellular compartment and could offset the intracellular

swelling force". Thus, a normally permeable ion such as sodium is made effectively impermeable, when confined to the extracellular compartment by active transport (double-Donnan system). It follows that sodium leaks into the cell at all times and this accounts for a substantial part of the basal metabolic rate (3). The cell volume is determined under these situations by the equilibrium between the pumping rate and the leakage of sodium into the cell (Pump-Leak hypothesis; [57]). Thus, any factors which contribute to an increased intracellular sodium leakage increase the energy demand upon tne cell and cause it to swell. By the same token, swelling may occur through any circumstances reducing the rate of pumping, such as direct inhibition of the sodium pump (81). This depicts a much more dynamic and precariously balanced system than that inferred from a discussion of blood flow thresholds. The critical flow threshold represents the minimum amount of oxygen required to keep the Na^+-K^+ transport system in balance with the net leakage of these ions.

Heat Production in Muscle

Heat production in muscle is a by-product of the ATP hydrolysed by three primary routes: a) mechanical work via myosin ATPase; b) Ca^{++} transport by the sarcoplasmic reticulum (SR) via Ca^{++}-Mg^{++} ATPase; and c) ion transport at the cell surface and the transverse tubule membranes via Na^+-K^+ ATPase. Under usual circumstances, most calculations indicate that these first two mechanisms of ATP hydrolysis account for most of the ATP consumed (98). During an isometric contraction, the Ca^{++} pump is responsible for about 25 - 35 % of the ATP

hydrolyzed (83) and during tetanus the sustained elevation of sarcoplasmic Ca^{++} concentrations increases the hydrolysis rate to 40 - 60 % of total ATP consumption. Release of Ca^{++} from the sarcoplasmic reticulum is triggered by an action potential (influx of Na^{+}) at the neuromuscular junction. The transverse tubule system (T-system) relays the signal to the SR where rapid Ca^{++} efflux occurs through a high-conductance calcium release channel (84). Relaxation of muscle is mediated by the Mg^{++}-dependent Ca^{++}-ATPase via rapid uptake of the Ca^{++} from the SR.

The breakdown of this regulated process is thought to be the mechanism operative in the muscle rigidity and uncontrolled heat production in malignant hyperthermia (32). Malignant hyperthermia is a muscular disorder of genetically predisposed individuals usually triggered by anesthesia and results in rapid and often fatal increases in body temperature.

Can Elevated Intracellular Sodium Trigger Ca++ Release?

Inhibition of the sodium pump by cardiac glycosides increases the force of myocardial contraction in congestive heart failure (89). One attractive model proposes that the net intracellular Ca^{++} concentration is increased (thereby increasing contractility) by inhibiting the sodium pump, which reduces the sodium concentration gradient across the cell membrane and reduces an exchange-coupled Ca^{++} efflux (51). This model suggests that elevated intracellular sodium levels would indirectly lead to stimulation of the Ca^{++}-ATPase. According to Schwartz et al. (75), the well-established steep slope of the sodium-calcium exchange mechanism (25) is consistent with the concept that only a very small increase in internal sodium is

required to bring about a large increase in intracellular calcium. This suggests that a decline in the transmembrane sodium gradient and an increase in intracellular calcium could trigger additional ATPase activity.

Factors that enhance Ca^{++}-ATPase activity would necessarily increase heat production, as recently described in the eye muscle of billfish (11). This tissue is specialized for heat production and for warming the brain and eyes of marlins, sailfish, and spearfish. Heat production may be associated with the ATP-dependent cycling of Ca^{++} at the sarcoplasmic reticulum and may be activated by the normal pathway for excitation of skeletal muscle (T- system). This pathway for metabolic heat production could be opened if the sodium pump were inhibited and if intracellular sodium stimulated the accumulation of intracellular calcium.

The concept emerging from this review, thus far, is that heat and exercise foster an increased permeability (leak rate) of cell membranes which increases the energy overhead by increasing the basal metabolic rate. This could lead to a lowering of the "energy charge" as evidenced by increased loss of adenine nucleotides and the production of uric acid. If these events worsened to the point of triggering the Ca^{++}-ATPase in some form of energy-wasting futile cycle, the situation would be serious and could lead to the type of energy collapse typical of swollen or infarcted cells. The following discussion focuses on triggering mechanisms peculiar to hyperthermia.

Basal Metabolism and the Sodium Leak

C. C. Gale (29) noted that investigators of thermoregulation at the turn of the

century found it useful to separate chemical thermogenesis from physical thermogenesis. Physical thermogenesis was exemplified by events such as muscular exercise or shivering, whereas the hypermetabolism of Grave's disease fell within the realm of chemical thermogenesis. Others (62) have adapted this concept to the energy-requiring cell functions of the brain. The cerebral metabolic rate or total energy consumption was considered to be the sum of the activation metabolism supporting synaptic transmission and the basal or residual metabolism. Active sodium transport is present in all cells and accounts for a high proportion of the total energy use (3,23) in resting cells (20 to 45%) as basal metabolic rate. Residual metabolism is defined as that which remains after a "flat EEG" has been produced with barbiturate intoxication, for example (3). Most of the activation energy of brain is related to Na^+-K^+ transport leaked during the generation of synaptic potentials (54). Recent experiments reviewed by Astrup (3) indicate that the intact brain "is a leaky system, in which the transport of Na^+ and K^+ ions, which constantly keeps pace with the leakage of these ions, accounts for about half of the energy consumption". Residual metabolism is effectively inhibited by hypothermia, which provides a thermal restriction of the sodium channels (see ref 3 for review) and provides good clinical protection of the brain during circulatory arrest. The effect of lidocaine is additive to the effect of hypothermia (7), indicating that lidocaine provides an additional block of the sodium channels whether these are restricted by hypothermia or not. These concepts are useful because they help formulate the following questions. If hypothermia restricts sodium channels and reduces basal metabolism, what does hyperthermia do? If the cost of the basal metabolism is

increased, what happens to our ability to sustain physical exercise?

Heating Rate and Physical Exhaustion

We have recently summarized a decade of research relating the rat's endurance capacity to the average rate of heat storage prior to exhaustion (39). These results (Fig.1) describe a "continuum", characterized by physical exhaustion (high total work output, low rate of temperature rise) at the upper left of the curve and heat collapse (low total work output, high rate of temperature rise) at the lower right. Heavy rats (500 g) run in the cold (5°C) stored heat at a very low rate (0.02°C · min^{-1}) and accomplished 56 kg·m of work (40). Average run time was 100 min, average T_{core} at exhaustion was 39.7°C, and there were no fatalities from the exhaustive work. In contrast, heavy rats run at room temperature (26°C), stored heat at a very high rate (0.07°C · min^{-1}), accomplished little work (32 kg·m) and suffered 65 % heatstroke mortality (average Tcore at exhaustion was 41.7°C). The difference in the heat storage rate (3.5 fold) was due to the increase in ambient temperature since other factors (body weight, grade, speed) were held constant.

FIGURE 1

Two groups of lighter (356 g, 237 g) rats were run at the same grade and speed in a 26°C environment (22), and a third group (419 g) was run in a 20°C environment (38). Work capacity again was related inversely to the rate of heat storage, because as the rate of heat storage increased (even independently of metabolic rate, 500 g> 419 g> 356 g), work capacity declined. Since heavier rats worked at a higher percentage of their aerobic capacity, at constant treadmill grade and speed, the rate of heat storage, appears to be a major determinant of work

capacity, rather than the rate of energy production. This suggests that the heat the cell experienced (i.e. stored heat) could have reduced metabolic efficiency as a function of work capacity.

Physostigmine, a reversible cholinesterase inhibitor (90), causes acetylcholine to accumulate at cholinergic receptor sites. This produces an exaggeration of the normal response, which is equivalent to excessive cholinergic stimulation throughout the body. We (61) reasoned that this would superimpose an inefficient energy drain at the cellular level by stimulating increased sodium leakage, especially at nicotinic-type effecters. Physostigmine administration (200 ug · kg^{-1}) produced a significant increase in heating rate and a significant reduction in endurance capacity (Fig 1). These results are considered especially significant because the proposed mechanism should have increased the rate of sodium pumping and is thought to be the source of the added heat storage at constant speed and grade (61).

Hyperthermia and Lactate

In 1974, MacDougal et al (55) used a water-perfused suit to alter the rate of core temperature change in six human volunteers during prolonged, exhaustive treadmill running. The results (Fig. 2) bear a striking similarity to those reported in Fig 1. As noted, the most rapid rise occurred in the hyperthermal condition, which increased the $\dot{V}O_2$ but decreased the performance time from 91 to 48 min. Stroke volume declined with time and was accelerated in the hyperthermal condition. The reader should note the striking similarities in the positive slopes of minute ventilation and venous lactate concentrations in Figure 2. A reduction in the efficiency of

Figure 2

energy metabolism was proposed as a possible explanation of the results. Similar findings were evident in a recent report of Owen et al. (63) but received no comment by the authors. We are impressed by the fact that lactate tracks heating rate in humans during constant work, and yet heating rate receives little or no comment in discussions of lactate metabolism (12,31,85,93). Jacobs (43) has pointed out that the onset of blood lactic acid accumulation is more highly correlated with running performance than other variables, including the maximal aerobic power. The high correlation between heating rate and lactate, and the highly significant inverse relationship between endurance capacity and heating rate, suggests that part of the observed variability in individual anaerobic threshold lactate concentrations (87) may be related to different rates of heat storage.

An extensive literature search (37,68) indicates that there is an inverse relation between temperature and pH. Acidosis in muscle decreases tetanic tension prolongs relaxation times (72), inhibits glycolysis via phosphofructokinase activity (91), depresses glycogenolysis (21), and reduces myocardial contractility (86). Acidosis also reduces the myocardial responsiveness to catecholamines (95) and depresses myofibrillar ATPase (26). In order to restore intracellular pH and the intracellular buffering capacity, hydrogen ions are exchanged for sodium ions (68); this is an energy requiring reaction because the sodium must be pumped from the cell or swelling occurs. Since acidosis increases serum potassium independently of total body potassium (14), acidosis creates an ionic imbalance across the muscle membrane with a tendency toward increased intracellular sodium and extracellular potassium. A change in the ionic composition of fatigued muscle in this direction

has been reported (70,83). We have hypothesized (37,39) that a thermally-driven influx of Na results in an additional energy drain, is superimposed on that caused by exhaustive work, and that a significant portion of this energy requirement could be due to stimulation of glycolysis to fuel a Na^+-H^+ exchange. The findings of Fink et al. (28) support this concept, in that glycogen depletion was greater during exercise in a hot (versus cold) environment.

Does Glycolysis Fuel the Sodium Pump?

The continued production and catabolism of lactate during rest (36,50), as well as exercise (36,42), attacks the fundamental premise that lactate reflects an oxygen debt or an anaerobic component. A recent review (12) has emphasized that lactate production is not necessarily associated with muscle anaerobiosis but is seen to play a profound role in the carbohydrate metabolism of resting individuals by converting much of the glucose undergoing glycolysis to lactate, which serves as a substrate for glycogen synthesis by the liver (the "glucose to liver glycogen pathway"). Sahlin (69) has suggested that glycolysis has two distinct advantages over aerobic ATP production: it can accelerate from resting to a maximal rate in a shorter time and the maximal rate of ATP formation is about 2-fold higher. The speed with which ATP production can be increased via glycolysis appears uniquely suited to fuel an ion pumping mechanism. Since the Na^+-K^+ ATPase is located within the cell membrane (89), the ADP and Pi liberated by pump activity may stimulate glycolysis directly (69). This model does not require that oxygen availability be decreased, to account for active glycolysis. If heat stimulates the

sodium pump by increased sodium leakage and increased Na^+-H^+ exchange, then increased glycolysis would generate lactate as reducing equivalents (reduced coenzymes) accumulated within the cytoplasm, reflecting the fact that the mitochondrial oxidative capacity had been exceeded by the rate of glycolysis (44).

The Sodium Pump

As recently discussed by Lechene (53), "the essential importance of the physiological role of the Na^+-K^+ pump transcends any particular domain of physiology" because it is "a universal energy transducer...[which] allows cells to perform their general and their terminally differentiated functions and is at the core of all organ activity". The rate of leaking and of pumping may vary by two orders of magnitude among cell types and may vary by 3 - 4 fold within a cell type (53). The more metabolically active cells leak more, in order to take advantage of the potential energy of the ionic chemical gradients, to move various substances into (phosphate, amino acids, glucose) and out of (protons, calcium, bicarbonate) the cell. Thus, more metabolic activity presumes a higher leaking and pumping activity. If the increase in sodium influx is sustained, there is an increase in both the Na^+-K^+ pump rate and the synthesis of new pumps (53). This fact certainly should stimulate interesting research in the area of endurance training and heat acclimation. The Na^+-K^+ pump resides within the membrane as one component in a multi-enzyme complex (66), including glyceraldehyde-3-phosphate dehydrogenase (GAPD) (73) and phosphoglycerate kinase (PGK) which can function to produce ATP (65,74). As shown in Figure 3, the ATP produced by this multi-enzyme complex is

FIGURE 3

compartmentalized (64,65) and forms an ATP pool that can be preferentially utilized by the Na^+-K^+ pump (66). The type of compartmentalized pool described for red cells has yet to be established in other cell types, but provides strong evidence that heat-stimulated lactate production is related to sodium leakage and thermally-stimulated glycolysis. It is still a matter of speculation whether bulk ATP from within the cell has access to the Na^+-K^+ pump or whether the only access of ATP to the Na^+-K^+ pump is via the membrane pool (66). This requirement for carbohydrate metabolism to support membrane pump activities has a profound impact on the ability to carry-out sustained exercise in the heat and could impact mechanical efficiency under hyperthermic conditions.

The Sodium Pump and Potassium Depletion

Clausen and Evert (19) recently asked whether the sodium pump capacity of skeletal muscle is inadequate during sustained work. Many observations (19) point to an appreciable net loss of cellular K^+, both in vivo and in vitro. This suggests that the excitation loss of K^+ during each a ction potential may exceed the capacity to reaccumulate K^+ by the Na^+-K^+ pump. The proposed net losses would become larger at higher stimulation frequencies and temperatures. This is the most likely explanation (19) for the net loss of K^+ from working muscle and the hyperkalemia seen during exercise (83). Sejersted (77) has made an important contribution to our understanding of the role of hypokalemia in the performance decrements and predisposition to heatstroke seen in potassium deficiency. Assuming Michaelis-Menten kinetics (77), a Km of 0.8 mM will cause 85 % of the activation

observed at an extracellular K^+ concentration of 4.5mM. Increments in plasma K^+ could only cause modest activation of the sodium pump, but hypokalemia could lower pump rate significantly. Hypokalemia would thus have a serious potential impact on the ability of the K^+-deficient individual to increase pumping, in the face of exercise hyperthermia.

Heatstroke and Potassium Depletion

In contrast to the physostigmine experiments, rats made potassium deficient via a low-potassium diet (38) exhibited exercise tolerance well below that predicted by the increased heat storage (-14 kg·m), suggesting a more profound functional incapacity (Fig 1). Knochel was the first to comment on the possibility that potassium depletion could be involved in the etiology of heatstroke (45). Conn (20) later suggested that heat acclimatization resembled mineralocorticoid escape; this since has been verified in subjects consuming high and low Na+ diets (1). In such circumstances, Knochel reasoned that elevated aldosterone levels, in combination with sodium intake, could cause renal potassium wasting. Subsequently, in 1972, Knochel et al (47) measured ^{42}K in six volunteers undergoing intensive physical conditioning in a hot climate and estimated a mean potassium deficit of 517 mEq on training day eleven.

Low serum potassium (< 4.0 mEq · l^{-1}) was found in 61% of the cases reported by Austin and Berry (9). In 1967, Shibolet et al. (78) examined serum potassium in 31 of 36 patients and with few exceptions the values were low (22 below

4.0 mEq · l^{-1}; 71 %). By 1976, Knochel and Carter (46), while exploring the pathogenesis of acute renal failure following prolonged hard work in hot climates, noted that serum potassium was low in about 50 % of the cases, despite the occurrence of muscle injury. The finding of hypokalemia coexisting with acute muscle necrosis and metabolic acidosis suggested preexisting whole body K^+ deficiency. In K^+-depleted dogs (49), muscle weakness occurred when animals had lost approximately 20 % of their total body potassium. As K^+ deficiency advanced to 30 %, the muscle resting membrane potential fell sharply, coincidental with an increased CPK activity. At this time, muscle cell composition became grossly abnormal with a prominent increase in intracellular Na^+ and Cl^-. These interesting findings were explained by two potential mechanisms: 1. " either a decrease in the rate of sodium extrusion from the cell by depression of an electrogenic sodium pump" or 2. "an abnormally high permeability of the cell to sodium".

A summary of the salient features of our prior study (38) on the effect of low-potassium diet on rat exercise hyperthermia and heatstroke mortality is shown in Table 1. These results show that the fatalities in each group did significantly more work than survivors, but that low-K^+ rats, compared to controls, exhibited performance decrements. A striking finding was the 2 - 3 fold increase in heating rate per unit of work output. The dramatic post-exercise increases in circulating potassium (> 90 %) in severely injured K^+-deficient animals raised plasma K^+ to normal control levels. This would make the prior state of hypokalemia difficult to diagnose. These results are entirely consistent with an inhibited pump mechanism in the K^+-deficient animals (and control group fatalities), which would compromise

TABLE 1

their ability to retain intracellular K^+. The marked elevation of heating rate in K^+-deficient animals is also consistent with a proposed increase in intracellular sodium, stimulating a Ca^{++}-dependent, energy wasting, futile cycle which reduces physical performance.

It is not known whether the Energy Depletion Model of heatstroke pathophysiology will be validated. It will be sufficient if the many avenues of cellular research raised by this review are considered in future studies of exercise hyperthermia.

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Disclaimer

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as official Department of the Army position, policy, or decision, unless so designated by other official documentation. In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Laboratory Animal Facilities and Care Committee, Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

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Figure legends

Figure 1. Work done (kg·m) versus heat storage rate (°C · min^{-1}) for rats of different weights, exercised at different temperatures (see text for refs.). Physostigmine (PH) was administered prior to running. Low K represents a group of rats made hypokalemic by a low-potassium diet. The two experimental groups (PH, Low K) are connected to their corresponding control groups by a broken line. Redrawn from Hubbard et al. (39).

Figure 2. Rectal temperature (n = 4), mean venous lactate concentrations and minute ventilatory volumes (n = 6) of six subjects during prolonged exhaustive treadmill running under three thermal states: normal, hyperthermal, and hypothermal. Treadmill speed was identical under each condition and was set at approximately 70 % of each subject's maximum aerobic power. Reproduced from Hubbard and Armstrong (37), with permission of the publisher.

Figure 3. A scheme representing the membrane organization of GAPD and PGK in association with the Na^+-K^+ pump in human red blood cells. Addition of the substrates in this figure generates ATP within the membrane pool that is preferentially utilized by the Na^+-K^+ ATPase. Redrawn from Gick, Ismail-Beigi, Edelman (30), and Proverbio, Shoemaker, Hoffman (66).

TABLE 1. Effect of low-K^+ diet on rat treadmill performance, heating rate and plasma potassium

Group	Work Done, kg · m		Change in Tc · (kg.m^{-1}), °C		Plasma K^+, mEq · l^{-1}	
	Control	Low K	Control	Low K^+	Control	Low K^+
Postrun survivors	53 ±20	26* ±14	0.05 ±0.04	0.12* ±0.06	6.3 ±1.1	3.7*! ±0.8
n	21	57	20	55	19	53
Postrun fatalities	78! ±29	33*! ±14	0.05 ±0.02	0.14 ±0.01	10.6 ±2.7	5.9*! ±2.2
n	3	15	3	15	2	8

Values are means ± SD.
* Low-K values significantly different from controls ($p<0.05$).
! Fatality values significantly different from survivors ($p<0.05$).
Data reformatted from Hubbard et al. (38).

Figure 1

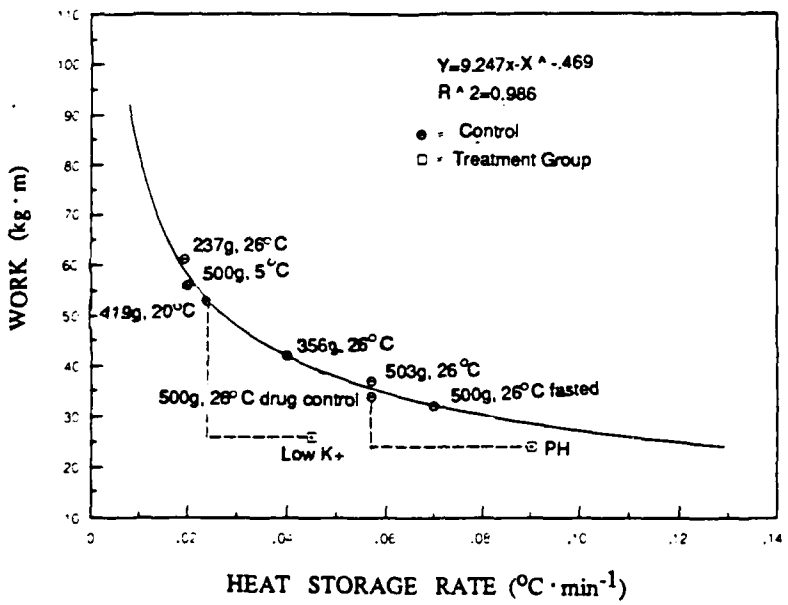
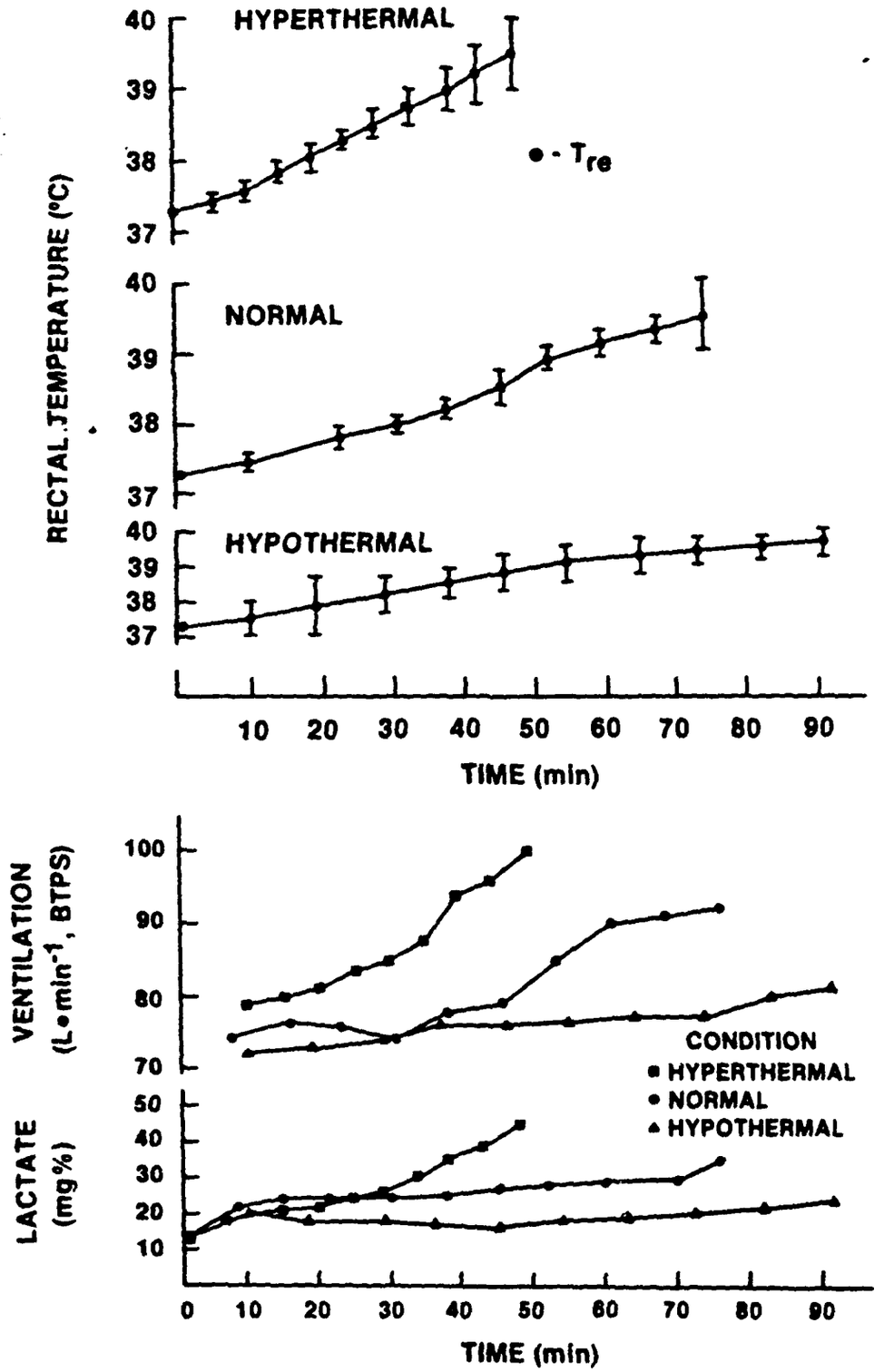

Y=9.247x-X ^ -.469
R ^ 2=0.986
● = Control
□ = Treatment Group
237g, 26°C
500g, 5°C
419g, 20°C
356g, 26°C
503g, 26°C
500g, 26°C fasted
500g, 26° C drug control
Low K+
PH
WORK (kg · m)
HEAT STORAGE RATE (°C · min⁻¹)

Figure 2


HYPERTHERMAL
NORMAL
HYPOTHERMAL
● - T_{re}
RECTAL TEMPERATURE (°C)
40
39
38
37
10 20 30 40 50 60 70 80 90
TIME (min)
VENTILATION (L•min^{-1}, BTPS)
100
90
80
70
LACTATE (mg%)
50
40
30
20
10
0 10 20 30 40 50 60 70 80 90
TIME (min)
CONDITION
■ HYPERTHERMAL
● NORMAL
▲ HYPOTHERMAL

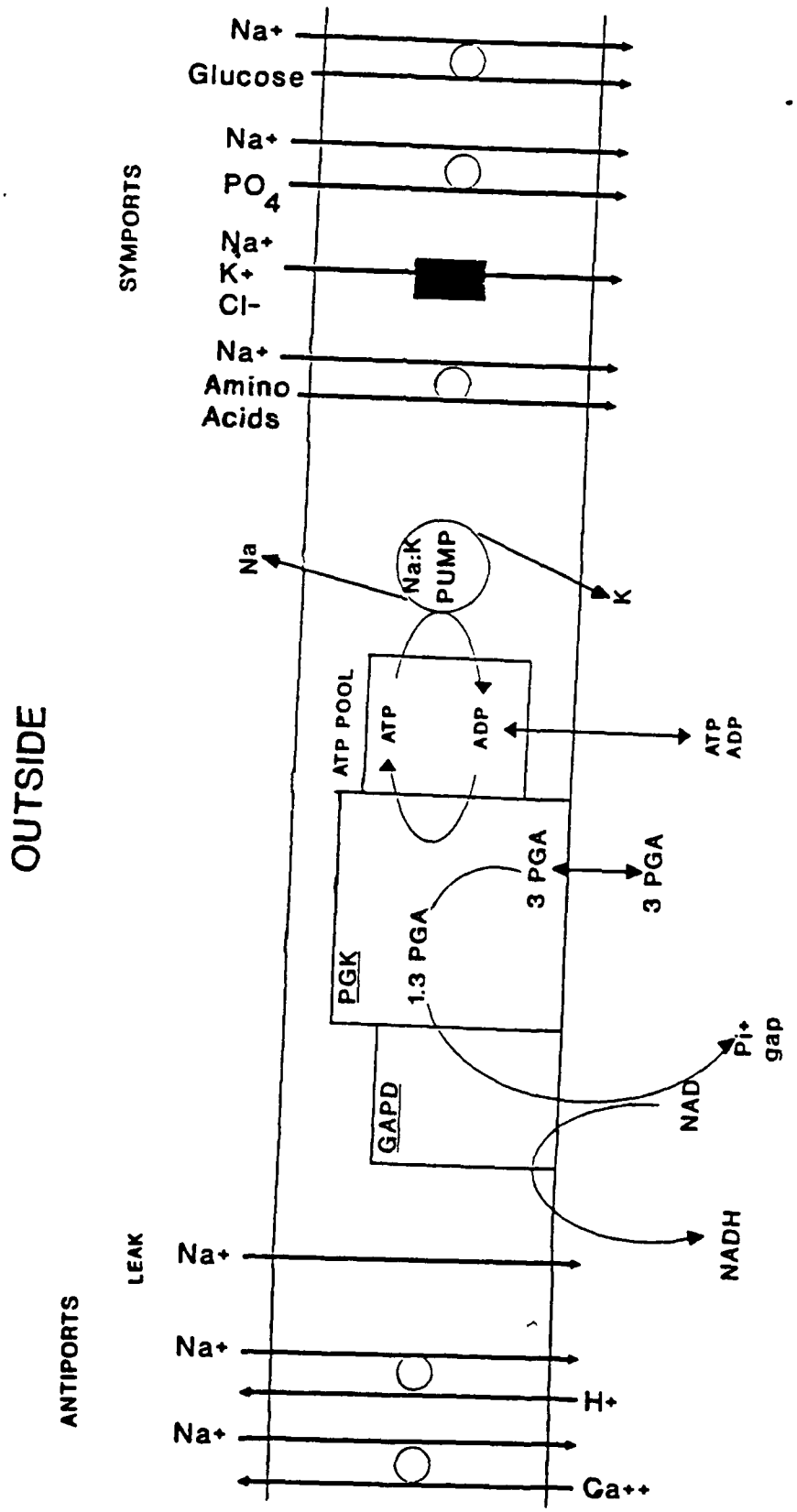

OUTSIDE
INSIDE
SYMPORTS
ANTIPORTS
LEAK
Na+
Glucose
Na+
PO4
Na+
K+
Cl-
Na+
Amino
Acids
Na
Na:K
PUMP
K
ATP POOL
ATP
ADP
ATP
ADP
3 PGA
3 PGA
1.3 PGA
PGK
GAPD
Pi+
gap
NAD
NADH
Na+
Na+
H+
Na+
Ca++

Figure 3